

CLINICAL RESEARCH

Clinical Trial

Carotid Artery Revascularization in High-Surgical-Risk Patients Using the Carotid WALLSTENT and FilterWire EX/EZ

1-Year Outcomes in the BEACH Pivotal Group

Sriram S. Iyer, MD, FACC,* Christopher J. White, MD, FACC,† L. Nelson Hopkins, MD,‡ Barry T. Katzen, MD,§ Robert Safian, MD, FACC,|| Mark H. Wholey, MD,¶ William A. Gray, MD, FACC,# Rocco Ciocca, MD,** William B. Bachinsky, MD, FACC,†† Gary Ansel, MD,‡‡ James D. Joye, DO, FACC,§§ Mary E. Russell, MD, FACC,** for the BEACH Investigators

New York and Buffalo, New York; New Orleans, Louisiana; Miami, Florida; Royal Oak, Michigan; Pittsburgh and Harrisburg, Pennsylvania; Natick, Massachusetts; Columbus, Ohio; and Mountain View, California

Objectives

The multicenter, single-arm BEACH (Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients) evaluated outcomes in high-surgical-risk patients with carotid artery stenosis treated with the Carotid WALLSTENT plus FilterWire EX/EZ Emboli Protection System (Boston Scientific, Natick, Massachusetts).

Background

Carotid artery stent (CAS) placement offers a less invasive alternative for high-risk surgical carotid endarterectomy (CEA) patients.

Methods

The trial enrolled 480 pivotal patients who were candidates for carotid revascularization but considered high surgical risk due to pre-specified anatomic criteria and/or medical comorbidities. The primary end point (all stroke, death, or Q-wave myocardial infarction [MI] through 30 days; non-Q-wave MI through 24 h; and ipsilateral stroke or neurologic death through 1 year) was compared with a proportionally weighted objective performance criterion (OPC) of 12.6% for published surgical endarterectomy results in similar patients, plus a pre-specified noninferiority margin of 4%.

Results

Among pivotal patients, 41.2% were at high surgical risk due to comorbid risk factors, and 58.8% due to anatomic risk factors; 76.7% were asymptomatic with flow-limiting carotid stenosis >80%. At 1 year, the composite primary end point occurred in 8.9% (40 of 447), with a repeat revascularization rate of 4.7%. With an upper 95% confidence limit of 11.5% for the primary composite end point, the BEACH trial results met the pre-specified criteria for noninferiority relative to the calculated OPC plus noninferiority margin (16.6%) for historical surgical CEA outcomes in similar patients ($p < 0.0001$ for noninferiority).

Conclusions

The BEACH trial results demonstrate that CAS with the WALLSTENT plus FilterWire embolic protection is non-inferior (equivalent or better than) to CEA at 1-year in high-surgical-risk patients (Boston Scientific Embolic Protection, Inc. [EPI]: A Carotid Stenting Trial for High-Risk Surgical Patients [BEACH]; <http://clinicaltrials.gov/ct2/show/NCT00316108?term=NCT00316108&rank=1>; NCT00316108). (J Am Coll Cardiol 2008;51:427–34)
© 2008 by the American College of Cardiology Foundation

Carotid artery disease is a major cause of ischemic stroke, with an absolute risk directly related to the severity of stenosis and presence of neurologic symptoms (1,2). Surgical removal of atherosclerotic plaque (carotid endarterec-

tomy [CEA]) can successfully reduce the incidence of cerebral infarction in both symptomatic patients and asymptomatic patients with carotid stenosis >60% (3–7). Some

From the *Lenox Hill Hospital, New York, New York; †Ochsner Clinic Foundation, New Orleans, Louisiana; ‡University of Buffalo, Buffalo, New York; §Baptist Hospital, Miami, Florida; ||William Beaumont Hospital, Royal Oak, Michigan; ¶Pittsburgh Vascular Institute, Pittsburgh, Pennsylvania; #Columbia University Medical Center, New York, New York; **Boston Scientific Corporation, Natick, Massachusetts; ††Pinnacle Health at Harrisburg Hospital, Harrisburg, Pennsylvania;

‡‡Riverside Methodist Hospital, Columbus, Ohio; and §§El Camino Hospital, Mountain View, California. The BEACH trial was supported by Boston Scientific Corporation. The current affiliation for Dr. Ciocca is University of Massachusetts Medical School, Worcester, Massachusetts. The current affiliation for Dr. Russell is Ascent Translational Sciences, Carlisle, Massachusetts.

Manuscript received July 23, 2007; revised manuscript received September 4, 2007, accepted September 17, 2007.

Abbreviations And Acronyms
CAS = carotid artery stent/stenting
CCA = common carotid artery
CEA = carotid endarterectomy
CI = confidence interval
FDA = Food and Drug Administration
ICA = internal carotid artery
MI = myocardial infarction
NIHSS = National Institutes of Health Stroke Scale
OPC = objective performance criterion
PSV = peak systolic velocity

patients, however, are unable to safely undergo CEA due to unfavorable anatomy or comorbid conditions (8–11), and are increasingly considered for treatment by carotid artery stent (CAS) placement with cerebral embolic protection (12–19). The BEACH (Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients) trial is an ongoing, prospective, multicenter, single-arm trial evaluating the outcomes of high-surgical-risk patients treated with the Carotid WALLSTENT and either the FilterWire EX or FilterWire EZ Emboli Protection System distal filter device (Boston Scientific Corp., Natick, Massachusetts). Thirty-day outcomes for the pivotal group were reported previously (20); this report discusses 1-year pivotal outcomes.

Methods

Study design. The BEACH trial was designed to test if outcomes in high-surgical-risk patients treated with the WALLSTENT plus FilterWire EX/EZ would be non-inferior to a calculated objective performance criterion (OPC) agreed upon with the U.S. Food and Drug Administration (FDA). The primary end point was 1-year composite morbidity and mortality. Noninferiority was assessed by comparing the upper 95% confidence interval (CI) of the observed end point to a literature-derived OPC for CEA in patients with similar demographics, with a pre-specified noninferiority margin (delta) of 4%.

Patients were enrolled into a roll-in phase to familiarize physicians with the protocol and devices (first 1 to 9 patients per site), a pivotal phase, or a bilateral registry (patients requiring treatment for both carotid arteries). After review of roll-in periprocedural outcomes, investigators were allowed to proceed to the pivotal phase. This report discusses 1-year outcomes, but study patients continue to be monitored through 3 years of follow-up.

Patient selection, device, procedure, and follow-up. Details of patient selection, device, procedure, and follow-up have been described (20). Briefly, eligible patients with carotid disease met general inclusion criteria plus at least 1 definition of surgical high risk based on specific anatomic and comorbid clinical criteria (Table 1). The common carotid artery (CCA), bifurcation, or internal carotid artery (ICA) was 4 to 9 mm in diameter, with ≥50% stenosis by angiography in symptomatic patients and ≥80% in asymptomatic patients as determined by the operator (visual

Table 1	Major Eligibility Criteria
Inclusion criteria	
General criteria	
Age ≥18 yrs	
Unilateral or bilateral atherosclerotic or restenotic lesions in native CCA, ICA, or carotid bifurcation	
Symptoms plus stenosis ≥50% of the luminal diameter by angiography	
No symptoms plus stenosis ≥80% of the luminal diameter by angiography	
Target segment reference diameter ≥4.0 and ≤9.0 mm	
Vessel diameter distal to target lesion ≥3.5 and ≤5.5 mm as an optimal “landing zone” for the FilterWire	
Life expectancy ≥1 yr post-index procedure	
Criteria for high-risk	
Anatomic high-risk category (1 criterion required)	
Restenosis post-carotid endarterectomy	
Contralateral total occlusion with a qualifying lesion on the ipsilateral side	
Previous neck or head radiation therapy/surgery including area of stenosis	
Surgically inaccessible lesions at or above C2 or below clavicle	
Spinal immobility of neck	
Tracheostoma	
Laryngeal palsy or laryngectomy	
Comorbid high-risk category 1 (1 criterion required)	
Unstable angina (CCS class III/IV)	
Left ventricular ejection fraction ≤30%	
Congestive heart failure (NYHA functional class III/IV)	
Planned coronary artery bypass graft or valve replacement post-carotid index procedure	
Chronic obstructive pulmonary disease manifested with forced expired volume ≤30%	
Comorbid high-risk category 2 (2 criteria required)	
Age ≥75 yrs	
Major diseased coronary arteries (≥2) with ≥70% stenosis (patients with angina)	
Planned peripheral vascular surgery, or other major surgeries post-carotid stenting	
Myocardial infarction ≥72 h and ≤30 days	
Exclusion criteria	
Patient experienced evolving, acute, or recent stroke within 21 days of study evaluation	
Patient experienced a major stroke (NIHSS score ≥15)	
Known cardiac sources of emboli likely to be associated with cerebral ischemic events	
Myocardial infarction <72 h before the index procedure	
Any surgery requiring general anesthesia ≤30 days preceding stent procedure	
Total occlusion of ipsilateral carotid artery	
Pre-existing stent in ipsilateral carotid artery or in a contralateral vessel ≤30 days before procedure	
Severe tandem lesions that cannot be covered with 1 stent	

CCA = common carotid artery; CCS = Canadian Cardiovascular Society; ICA = internal carotid artery; NIHSS = National Institutes of Health Stroke Scale; NYHA = New York Heart Association.

estimate) per NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria (7). The protocol was approved by institutional review boards of the 47 participating U.S. institutions; written informed consent was obtained from patients before enrollment, and the trial complied with the Declaration of Helsinki. Trial results are reported on the National Institutes of Health website.

Election of stent size (Carotid WALLSTENT Monorail Endoprosthesis, Boston Scientific Corp.) and emboli pro-

tection length and placement (FilterWire EX or FilterWire EZ Embolic Protection System, Boston Scientific Corp.) were based on the operator’s visual estimate of vessel diameter. At the end of the procedure, the filter together with any contained material was collapsed and retrieved. All patients were examined before (within 7 days) and after the procedure (per protocol, within 24 h and at the time of any change in clinical symptoms) by an independent neurologist or neurosurgeon certified in the administration of the National Institutes of Health Stroke Scale (NIHSS). Patients were also monitored continuously during the procedure and frequently during the in-hospital recovery period by physician and nursing staff, including neurologic examinations. All patients underwent carotid duplex ultrasonography before the procedure and before discharge. Investigator training included review of animal studies, on-site proctoring to achieve competence in device implantation, and general training on the protocol. Independent ultrasound and angiographic core laboratories provided review of all studies throughout the course of the trial and validation of site-determined entry criteria. Follow-up included carotid duplex ultrasonography as well as independent neurologic examination using the NIHSS at 1, 6, and 12 months and yearly thereafter through 3 years.

Primary end point. The primary composite end point included all stroke, death, and Q-wave myocardial infarction (MI) through 30 days; non-Q-wave MI through 24 h; and ipsilateral stroke and neurologic death through 1 year. Adverse events were adjudicated by an independent clinical events committee. Analyses of all measurements obtained were performed according to published criteria by core laboratories (Online Appendix 1) (20).

Statistical analyses. Harvard Clinical Research Institute (Online Appendix 1) performed data management and statistical analyses with SAS version 8.2 or above (SAS Institute

Table 3 Patient and Lesion Baseline Characteristics	
Characteristic	Value (n) *
Patient	
Age, in yrs†	70.9 ± 9.3 (480)
Male gender (%)	65.2 (313)
History of cerebrovascular accident (%)	28.1 (135)
History of transient ischemic attack (%)	30.4 (146)
Previous carotid endarterectomy (%)	40.6 (195)
History of congestive heart failure (%)	21.7 (103)
Prior myocardial infarction (%)	35.4 (170)
History of hypertension (%)	89.4 (429)
Current/prior smoking (%)	74.6 (358)
Lesion	
ICA (% patients)	88.3% (424)
CCA (% patients)‡	11.7% (56)
Lesion length (mm)†	15.1 ± 7.2 (480)
De novo (%)	66.0% (317)
Diameter stenosis (%)†	71.6 ± 10.7 (479)
ICA/CCA ratio†	5.3 ± 3.1 (420)

*n = 480; †mean ± standard deviation; ‡bifurcation lesions for this analysis were included under the CCA category.
Abbreviations as in Table 1.

Inc., Cary, North Carolina). Freedom from 1-year morbidity and mortality was determined by Kaplan-Meier analysis; predictors were identified using single- and multi-variable logistic regression analyses (p < 0.05 for significance).

In the BEACH trial, CAS was compared to CEA (control) to determine if stenting was non-inferior to surgery in the high-surgical-risk patient population. The CEA comparator was a calculated OPC applied to the primary composite end point. The mathematical equation (in the following text) representing the OPC was derived using data in the literature (Online Appendix 2) from CEA outcomes in high-surgical-risk patients and reflects the

Table 2 Pivotal Group Patient Qualification by High-Risk Criteria	
Condition*	Percent (n)
Anatomic high-risk conditions	
Restenosis post-carotid endarterectomy	34.2% (164)
Contralateral total occlusion with a qualifying lesion on the ipsilateral side	18.1% (87)
Previous neck or head radiation therapy or surgery that included the area of stenosis/repair or ipsilateral radical neck dissection for cancer	10.8% (52)
Comorbid conditions (1 criterion qualifies)	
Unstable angina (CCS class III/IV)	12.5% (60)
Known severe LVEF (≤30%)	12.1% (58)
Congestive heart failure (NYHA functional class III/IV)	11.7% (56)
Comorbid conditions (2 criteria qualifies)	
Age ≥75 yrs	39.0% (187)
Two or more major diseased coronary arteries with ≥70% stenosis at the time of index procedure in patients with a history of angina	21.7% (104)

*≥10% of patients; n = 480.
LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

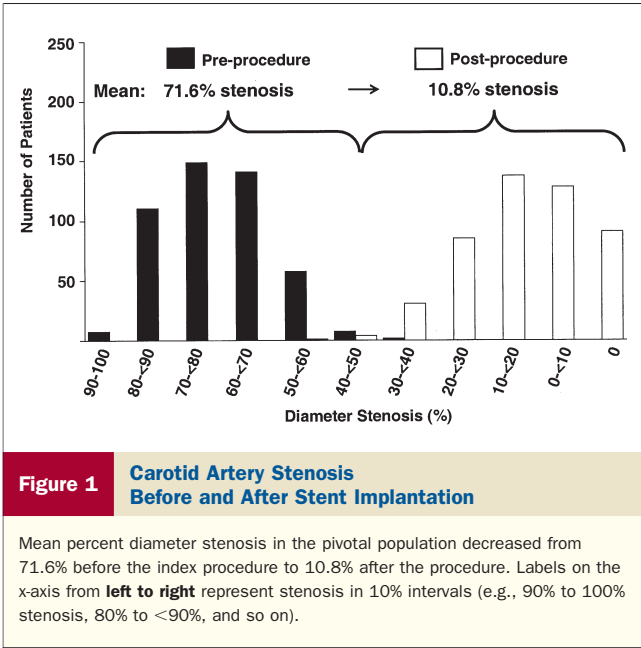


Figure 1 Carotid Artery Stenosis Before and After Stent Implantation

Mean percent diameter stenosis in the pivotal population decreased from 71.6% before the index procedure to 10.8% after the procedure. Labels on the x-axis from left to right represent stenosis in 10% intervals (e.g., 90% to 100% stenosis, 80% to <90%, and so on).

Table 4 Primary End Point—Pivotal Group

Event	Rate (%) [*]	95% CI
One-year morbidity and mortality†	8.9% (40)	11.5%‡
Non-Q-wave MI (through 24 h)	0.9% (4)	(0.2%–2.3%)
Death, stroke, Q-wave MI (through 30 days)	5.4% (24)	(3.5%–7.9%)
Death	1.6% (7)	(0.6%–3.2%)
Stroke	4.5% (20)	(2.8%–6.8%)
Ipsilateral	3.4% (15)	(1.9%–5.5%)
Major ischemic	1.1% (5)	(0.4%–2.6%)
Minor ischemic	2.0% (9)	(0.9%–3.8%)
Hemorrhagic	0.2% (1)	(0.0%–1.2%)
Contralateral	1.1% (5)	(0.4%–2.6%)
Major ischemic	0.0% (0)	(0.0%–0.8%)
Minor ischemic	0.7% (3)	(0.1%–2.0%)
Hemorrhagic	0.4% (2)	(0.1%–1.6%)
Q-wave MI	0.2% (1)	(0.0%–1.2%)
Neurologic death, ipsilateral stroke (31 to 360 days)	3.1% (14)	(1.7%–5.2%)
Neurologic death	1.6% (7)	(0.6%–3.2%)
Ipsilateral stroke	2.5% (11)	(1.2%–4.4%)

^{*}n = 447 at 1 year; †based on adjudicated events in evaluable patients through 360 days; ‡1-sided upper confidence interval (CI). Numbers are % (n).
MI = myocardial infarction.

calculated surgical risk associated with anatomical conditions ($\pi_{\text{OPC}} - \text{Anatomical}$) plus that associated with comorbid conditions ($\pi_{\text{OPC}} - \text{Comorbid}$). The weighted OPC ($\pi_{\text{OPC}} - \text{Weighted}$), reflecting the calculated CEA risk for the BEACH primary end point, was obtained by multiplying the anatomical and comorbid risk by the percentage of BEACH patients in the surgical high risk anatomical (ω_A) and surgical high risk comorbid (ω_C) groups, respectively, as shown in the equation below.

With the concurrence of the U.S. FDA, 11% was selected as $\pi_{\text{OPC}} - \text{Anatomical}$ and 15% as $\pi_{\text{OPC}} - \text{Comorbid}$, with the higher risk assumed in cases qualifying for both. Using the enrollment percentages in each category (58.8% anatomical

[ω_A] and 41.2% comorbid [ω_C]), the calculated weighted OPC for this trial was 12.6%. Because true equivalency cannot be realized with less than an infinite sample size, an FDA-concurred pre-specified spread of 4% for the “delta” definition of equivalency was added to the weighted OPC to yield an upper noninferiority boundary of 16.6%. The BEACH primary composite end point with a 1-sided upper 95% CI was compared with this boundary (weighted OPC plus delta) to assess noninferiority of CAS to CEA. Statistical significance was determined using a normal approximation test for a single proportion (Z test).

Results

The BEACH trial enrollment began February 2002 and ended December 2003 with 189 roll-in phase patients, 78 patients in the bilateral registry, and 480 patients in the pivotal study group. The trial was temporarily suspended on December 24, 2002 due to carotid WALLSTENT malfunctions and re-initiated on June 11, 2003 after the cause of the malfunctions was identified and corrected. Of 47 centers participating (Online Appendix 3), 36 contributed to the pivotal group. Data for patients receiving the Filter-Wire EX and FilterWire EZ were pooled because there was no statistically significant difference in end points between these groups after adjustment for baseline percent diameter stenosis.

Baseline and procedural characteristics—pivotal group. Among pivotal patients, 41.2% had comorbid risk factors, and 58.8% had anatomical risk factors, resulting in a calculated noninferiority margin (OPC plus 4% delta) of 16.6% for the 1-year composite primary end point. Table 2 lists patient qualifications by individual high-risk criteria; Table 3 lists baseline patient and lesion characteristics. Over three-quarters of the patients (77%, 368 of 480) were asymptomatic; 99.2% of whom had site-reported (visual estimate) carotid stenosis between 80.0% and 99.9%. Quantitative

Table 5 Adverse Event Rates in the BEACH Pivotal Group Symptomatic and Asymptomatic Patients

Event	Symptomatic Patients (n = 112) [*]		Asymptomatic Patients (n = 368)	
	Rate (%) [*]	95% CI	Rate (%)†	95% CI
1-yr morbidity and mortality‡	12.5% (13)	(6.8%–20.4%)	7.8% (27)	(5.2%–11.2%)
Non-Q-wave MI (through 24 h)	1.9% (2)	(0.2%–6.8%)	0.6% (2)	(0.1%–2.1%)
Death, stroke, Q-wave MI (through 30 days)	7.7% (8)	(3.4%–14.6%)	4.7% (16)	(2.7%–7.4%)
Death	1.0% (1)	(0.0%–5.2%)	1.7% (6)	(0.6%–3.8%)
Stroke	7.7% (8)	(3.4%–14.6%)	3.5% (12)	(1.8%–6.0%)
Major ischemic	1.9% (2)	(0.2%–6.8%)	0.9% (3)	(0.2%–2.5%)
Minor ischemic	3.8% (4)	(1.1%–9.6%)	1.5% (5)	(0.5%–3.4%)
Hemorrhagic	0.0% (0)	(0.0%–3.5%)	0.3% (1)	(0.0%–1.6%)
Q-wave MI	0.0% (0)	(0.0%–3.5%)	0.3% (1)	(0.0%–1.6%)
Neurologic death, ipsilateral stroke (31 to 360 days)	3.8% (4)	(1.1%–9.6%)	2.9% (10)	(1.4%–5.3%)
Neurologic death	1.9% (2)	(0.2%–6.8%)	1.5% (5)	(0.5%–3.4%)
Ipsilateral stroke	3.8% (4)	(1.1%–9.6%)	2.0% (7)	(0.8%–4.1%)

^{*}23.3% of the pivotal group population was symptomatic; †at 1 year, n = 104 symptomatic patients and n = 344 asymptomatic patients; ‡based on adjudicated events in evaluable patients through 360 days. Numbers are % (n).

Abbreviations as in Table 4.

analysis of percent diameter stenosis determined by the core lab for the entire pivotal group was $71.6 \pm 10.7\%$ (mean \pm standard deviation); this decreased to $10.6 \pm 14.4\%$ post-procedure (Fig. 1) with 99.8% of patients having $<50\%$ post-procedure stenosis. Procedure success—a composite end point based on patients in whom a system placement attempt was made and including system technical success (successful delivery, deployment, and retrieval of the devices; 98.3%); angiographic success (in-stent residual diameter stenosis $\leq 30\%$ post-procedure; 90.8%); and the absence of death, stroke, or MI within 24 h of the index procedure—was 87.6% (418 of 477).

Clinical outcomes—pivotal group. At 30 days the composite major adverse event rate of death, stroke, and Q-wave MI in the pivotal group was 5.4% (24 of 447) (Table 4). The 1-year primary composite end point was 8.9% (40 of 447 patients) (Table 4). The 1-sided 95% upper CI was 2.6%, resulting in an upper limit (central estimate plus 95% CI) of 11.5% for the BEACH primary end point. This value was below the control comparator of 16.6% (calculated OPC for similar CEA patients of 12.6% plus the pre-specified delta of 4%), thereby indicating noninferiority of CAS to CEA ($p < 0.0001$ for noninferiority).

Table 5 shows primary end point outcomes for asymptomatic and symptomatic patients. There were no significant differences in rates between the 2 groups though there was a weak trend towards a higher rate of the primary end point for symptomatic versus asymptomatic patients at 1 year (12.5% vs. 7.8%, respectively, $p = 0.14$). Patients qualifying for the trial with comorbid high-surgical-risk factors had a significantly higher 30-day event rate than did those with anatomical high-risk factors (14.3% vs. 5.3%, respectively, $p = 0.002$). Advanced age (≥ 75 years) was associated with significantly worse outcomes, including late neurologic death (Fig. 2).

Freedom from morbidity and mortality was 91.6% at 1 year with most events occurring at ≤ 30 days (Fig. 3). Outcomes from 31 to 360 days (Table 6) include a late neurologic event rate related to stenting of 2.7% (12 of 447).

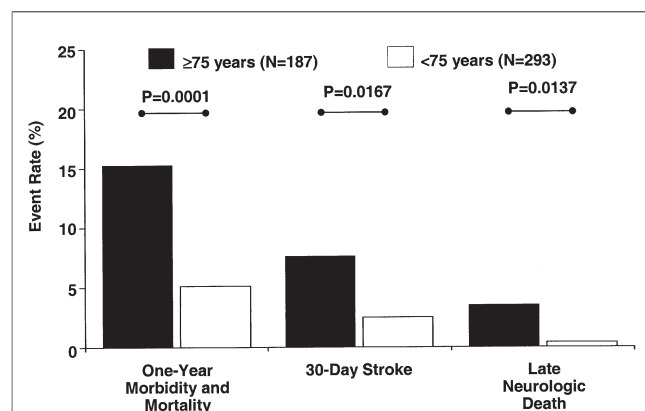


Figure 2 Significant Effects of Age on Outcomes

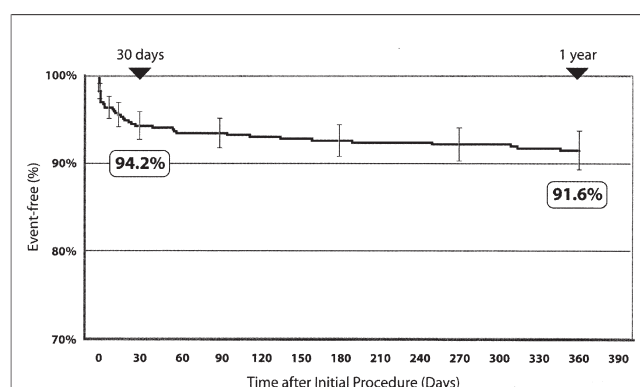


Figure 3 Freedom From Morbidity and Mortality (Kaplan-Meier Analysis)

The 1-year restenosis rate, defined as $\geq 70\%$ stenosis by duplex ultrasound, was 8.9% (40 of 447), with a 1-year repeat target vessel revascularization rate of 4.7% (20 of 425) including 17 asymptomatic patients with repeat revascularization driven by duplex findings alone. Per the BEACH trial protocol, a carotid angiogram was required if the duplex ultrasound demonstrated a restenosis of $\geq 70\%$. This potentially increased the re-intervention rate above what would be expected for this primarily asymptomatic group.

Predictors of 1-year morbidity and mortality—pivotal group. By univariate analysis, age ≥ 75 years ($p = 0.0004$) and the comorbid risk category ($p = 0.0017$) were significant predictors of 1-year morbidity and mortality. Multivariate analysis identified these same significant predictors ($p = 0.0002$ and $p = 0.0092$, respectively) plus diabetes ($p = 0.0357$) and symptomatic status ($p = 0.0774$).

Durability of revascularization—ultrasound results in the pivotal group. The ICA/CCA peak systolic velocity (PSV) ratio (mean \pm standard deviation) before the procedure was 5.3 ± 3.1 . This improved to 1.4 ± 0.5 immediately after the procedure and remained improved at 6 months (1.9 ± 1.2) and 1 year (1.9 ± 1.1). Additionally, there was no progression of ICA PSV_{maximum} over the latter 6 months of follow-up (Table 7).

Discussion

This prospective, multicenter, single-arm trial compared the outcomes of carotid stenting with a distal emboli protection filter to a calculated OPC based on the historical rate of

Table 6 Late Neurologic Events

Event (31 Through 360 days)	Number
Neurologic death and/or ipsilateral stroke	14
Neurologic death plus ipsilateral stroke*	5†
Neurologic death not related to ipsilateral stroke*	2
Ipsilateral stroke without death‡	7†

* 7 neurologic deaths occurred between 34 and 197 days post-intervention; † related to stenting; ‡ 7 ipsilateral strokes without neurologic death occurred between 40 and 346 days.

similar end points in high-surgical-risk patients undergoing CEA. The observed composite 1-year morbidity and mortality rate was 8.9%, with a 95% 1-sided upper confidence limit extending to 11.5%. This was significantly ($p < 0.0001$) below the 16.6% noninferiority boundary defined as the 12.6% historical rate in comparable surgical patients plus the pre-specified noninferiority margin of 4%. Therefore, the BEACH trial demonstrates that this form of CAS with distal embolic protection using the WALLSTENT in combination with the FilterWire emboli protection system is noninferior to (equivalent or better than) surgical CEA in high-surgical-risk patients (18,19).

Moreover, most of the morbidity and mortality in the 1-year primary end point was due to early events. The rate for death, stroke, and Q-wave MI was 5.4% (CI 3.5% to 7.9%) through 30 days; most events (3.4% [CI 2.8% to 6.8%]) were ipsilateral stroke (major [1.1%], minor [2.0%], hemorrhagic [0.2%]) (20). This is similar to the 4.8% rate of death, stroke, or MI in the randomized SAPHIRE (Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy) trial, which included 29.9% symptomatic patients in the stenting arm (18). The rate for symptomatic BEACH patients (7.7%) is similar to the 30-day event rate in 2 recent prospective randomized clinical trials of symptomatic carotid occlusive disease patients that failed to show a benefit of stenting over surgery (21,22). In the SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy) trial, the 30-day 6.8% rate of death or ipsilateral ischemic stroke in the stenting arm was not statistically different from the 6.3% rate in the CEA arm, and failure to demonstrate noninferiority of CAS to CEA despite similar event rates reflects premature termination of enrollment at 1,183 patients, resulting in inadequate statistical power (21). The EVA-3S (Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) trial reported a 9.6% incidence of any stroke or death in the stenting arm at 30 days with a corresponding CEA rate of 3.9%, possibly reflecting relative inexperience of CAS operators compared with very experienced surgical operators, as well as premature termination of the trial for safety concerns (22). In addition, comparison between U.S. and European studies may be limited as there is no distinction between patients considered high-risk or non-high-risk for surgery outside the U.S. The results of these 2 symptomatic trials, thus, are

outliers from the lower CAS rates seen in most of the high-surgical-risk carotid stenting trials.

In the BEACH trial, carotid duplex ultrasound at 6 months and 1 year indicated continued vessel patency, as reflected in a 1-year restenosis rate of 8.9%, a target vessel revascularization rate of 4.7%, and a stent-associated late neurologic event rate of 2.7%. The overall 8.6% composite 1-year end point in the BEACH trial also compares favorably to earlier trials. In the SAPHIRE trial, the primary end point (death, stroke, or MI at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year) was 12.2% (18). In the high-risk stent registry ARCHeR (Acculink for Revascularization of Carotids in High Risk Patients) (23.8% symptomatic patients), the primary end point (death, stroke, MI at 30 days plus ipsilateral stroke at 1 year) was 9.6% (19). In this high-risk patient population, confounding coronary and pulmonary morbidities are common, but their influence is limited by the use of a 1-year end point restricted to neurologic death and ipsilateral stroke beyond 30 days. The concordance in pure neurologic outcomes for the BEACH trial and 1-year results reported in 2 other large studies involving carotid stenting and high-surgical-risk patients with similar end points indicates that CAS can be reproducibly achieved in this patient population.

Older age was identified as a significant predictor of poor outcome as patients 75 years or older experienced higher event rates. Increased procedural risk may be attributable, in part, to a number of factors commonly associated with advanced age including excessive vessel tortuosity, arch elongation, and heavy calcification, which also contribute to increased risk with stent placement (23). Plaque burden is presumed to increase with age, leading to more events in the elderly population independent of intervention (24). In the lead-in phase of the CREST (Carotid Revascularization Endarterectomy vs. Stent Trial) (30.7% symptomatic), octogenarians exhibited increased complications at 30 days with CAS (25). Higher risk has been seen in elderly patients for both stenting and surgery, although improved devices and experience in CAS along with better patient selection have led to reductions in perioperative morbidity (26–33). Advances notwithstanding, the observed CAS results in older patients highlight the need to use CAS with distal emboli protection predominantly in patients at low risk for stenting, unless their risks for CAS are elevated to an even greater degree. Trials that enroll a high proportion of high

Table 7 Internal Carotid Artery Maximum Peak Systolic Velocity				
Pivotal Group	Time Point*			
	Pre-Procedure	Post-Procedure	6 Months	1 Year
ICA PSV _{max}	346.1 ± 148.0, 436, 332.2–360.0	115.8 ± 40.7, 452, 112.1–119.6	146.9 ± 73.5, 406, 139.8–154.1	138.8 ± 66.6, 370, 132.0–145.6

*Values are mean ± standard deviation (cm/s), n, 95% confidence interval.
ICA = internal carotid artery; PSV_{max} = maximum peak systolic velocity.

stent risk patients would similarly be expected to show higher complication rates, and operators should remember that medical management, in fact, may be a better choice for patients deemed high risk for *both* CAS and CEA (34).

It is critical to recognize that there has been a tremendous amount of progress made since the BEACH trial was initiated in 2002 regarding patient selection as a determinant of CAS outcomes. While the BEACH trial was designed to evaluate patients considered high risk for endarterectomy, it did not exclude those patients who would be considered high risk for *stenting*; the BEACH trial met the primary end point with a major adverse event rate below the FDA-agreed OPC. In asymptomatic patients with severe carotid stenosis, the 30-day event rate was 4.7%, which compares favorably with the asymptomatic SAPPHIRE group (5.4%) (18). However, recently drafted multispecialty consensus statements have concluded that with improved understanding of appropriate patient selection, the acceptable 30-day event rates for carotid stenting should be $\leq 3\%$ for asymptomatic patients and $\leq 6\%$ for symptomatic patients (35). The adoption of CAS as a minimally invasive alternative to CEA will be dependent upon both proper patient selection and appropriate physician training and experience. Further clinical trials should, thus, evaluate patients who are considered low or normal risk for both CEA and CAS—the majority of patients with carotid artery occlusive disease. Only positive results from this type of trial will move CAS from a niche procedure to a mainstream treatment option or the dominant standard of care.

Conclusions

The 1-year primary end point of 8.9% (upper confidence limit of 11.5%) for carotid stenting and emboli protection in high-surgical-risk patients treated in the BEACH trial meets the criteria for noninferiority to the 16.6% severity-adjusted surgical OPC plus delta. In high-surgical-risk patients who meet indications for carotid revascularization, CAS with emboli protection is not inferior to CEA at 1 year.

Acknowledgments

The authors thank Alex Shih, BS, Lynne Kelley, MD, and Ruth Starzyk, PhD (Boston Scientific Corp.), for their assistance in the statistical analyses (A.S.) and in drafting this manuscript (L.K. and R.S.).

Reprint requests and correspondence: Dr. Sriram Iyer, Lenox Hill Hospital, 130 East 77th Street, Black Hall, 9th Floor, New York, New York 10021. E-mail: SRIUAB@aol.com.

REFERENCES

- Barnett HJM, Taylor DW, Eliasziw M, et al. Causes and severity of ischemic stroke in patients with internal carotid artery stenosis. *JAMA* 2000;283:1429–36.
- Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis: North American symptomatic carotid endarterectomy trial collaborators. *N Engl J Med* 2000;342:1693–700.
- Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491–502.
- Barnett HJM, Taylor W, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415–25.
- European Carotid Surgery Trialists' Collaborative Group. Randomized trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European carotid surgery trial. *Lancet* 1998;351:1379–87.
- Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery disease. *JAMA* 1995;273:1421–8.
- North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. *N Engl J Med* 1991;325:445–53.
- Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* 2003;34:2290–303.
- Ouriel K, Hertzner NR, Beven E, et al. Preprocedural risk stratification: Identifying an appropriate population for carotid stenting. *J Vasc Surg* 2001;33:728–32.
- Shaw F, Kadro W, Domanski M, et al. Safety and efficacy of elective carotid artery stenting in high-risk patients. *J Am Coll Cardiol* 2000;35:1721–8.
- Wennberg D, Lucas F, Birkmeyer J, Bredenberg C, Fisher E. Variation in carotid endarterectomy mortality in the Medicare population. *JAMA* 1998;279:1278–81.
- Safian RD, Bresnahan JF, Jaff MR, et al., for the CREATE Pivotal Trial Investigators. Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol* 2006;47:2384–91.
- Goodney PP, Schermerhorn ML, Powell RJ. Current status of carotid artery stenting. *J Vasc Surg* 2006;43:406–11.
- Burton KR, Lindsay TF. Assessment of short-term outcomes for protected carotid angioplasty with stents using recent evidence. *J Vasc Surg* 2005;42:1094–100.
- Gray WA. Endovascular treatment of extra-cranial carotid artery bifurcation disease. *Minerva Cardioangiol* 2005;53:69–77.
- Alhaddad IA. Carotid artery surgery vs. stent: a cardiovascular perspective. *Catheter Cardiovasc Interv* 2004;63:377–84.
- Wholey MH, Wholey MH. History and current status of endovascular management for the extracranial carotid and supra-aortic vessels. *J Endovasc Ther* 2004;11 Suppl II:II43–61.
- Yadav JS, Wholey MH, Kuntz RE, et al., for the SAPPHERE Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;351:1493–501.
- Gray WA, Hopkins LN, Yadav S, et al., for the ARCHeR Trial Collaborators. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *J Vasc Surg* 2006;44:258–69.
- White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME, for the BEACH Trial Investigators. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv* 2006;67:503–12.
- The Space Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomized non-inferiority trial. *Lancet* 2006;368:1239–47.
- Mas J-L, Chatellier G, Beyssen B, et al., for the EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;355:1660–71.
- Roubin GS, Iyer S, Halkin A, Vitek J, Brennan C. Realizing the potential of carotid artery stenting: proposed paradigms for patient selection and procedural technique. *Circulation* 2006;113:2021–30.
- Störk S, van den Beld AW, von Schacky C, et al. Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. *Circulation* 2004;110:344–8.

25. Hobson RW II, Howard VJ, Roubin GS, et al., for the CREST Investigators. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg* 2004;40:1106–11.
26. Setacci C, de Donato G, Chisci E, et al. Is carotid artery stenting in octogenarians really dangerous? *J Endovasc Ther* 2006;13:302–9.
27. Stanziale SF, Marone LK, Boules TN, et al. Carotid artery stenting in octogenarians is associated with increased adverse outcomes. *J Vasc Surg* 2006;43:297–304.
28. Villalobos HJ, Harrigan MR, Lau T, et al. Advancements in carotid stenting leading to reductions in perioperative morbidity among patients 80 years and older. *Neurosurgery* 2006;58:233–40.
29. Roubin GS, New G, Iyer SS, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation* 2001;103:532–7.
30. McCrory DC, Goldstein LB, Samsa GP, et al. Predicting complications of carotid endarterectomy. *Stroke* 1993;24:1285–91.
31. Zahn R, Ischinger T, Hochadel M, et al., for the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). Carotid artery stenting in octogenarians: results from the ALKK Carotid Artery Stent (CAS) registry. *Eur Heart J* 2007;28:370–5.
32. Yen MH, Lee DS, Kapadia S, et al. Symptomatic patients have similar outcomes compared with asymptomatic patients after carotid artery stenting with emboli protection. *Am J Cardiol* 2005;95:297–300.
33. Marine LA, Rubin BG, Reddy R, Sanchez LA, Parodi JC, Sicard GA. Treatment of asymptomatic carotid artery disease: similar early outcomes after carotid stenting for high-risk patients and endarterectomy for standard-risk patients. *J Vasc Surg* 2006;43:953–8.
34. Narins CR, Illig KA. Patient selection for carotid stenting versus endarterectomy: a systematic review. *J Vasc Surg* 2006;44:661–72.
35. Bates ER, Babb JD, Casey DE, et al. ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting). *J Am Coll Cardiol* 2007;49:126–70.

▶ APPENDIX

For a list of core laboratories (Online Appendix 1), references used in the OPC calculation (Online Appendix 2), and investigators and institutions participating in the BEACH trial (Online Appendix 3), please see the online version of this article.